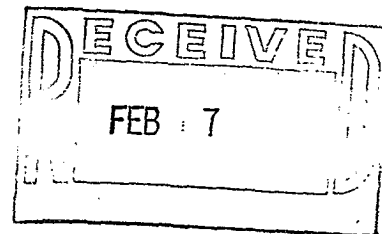
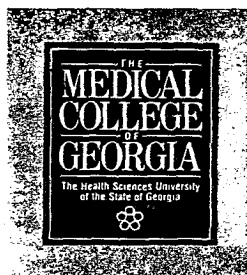


1
A



School of Medicine
Department of Physiology and Endocrinology

February 12, 1993

Harmon C. McAllister, Ph.D.
Research Director
Council for Tobacco Research, USA
900 3rd Avenue
New York, NY 10022

Dear Dr. McAllister;

I am an Associate Professor in the Department of Physiology and Endocrinology at the Medical College of Georgia. For the past 13 years, I have studied the regulation of gonadotropin secretion (luteinizing hormone and follicle stimulating hormone) from the anterior pituitary by steroids and hypothalamic releasing factors (luteinizing hormone releasing hormone). In the female mammal, the cyclic secretion of these hormones is essential for regulating the process of ovulation and thus maintenance of reproductive capacity. During a recent literature review, it became apparent that the role of tobacco (nicotine) in pituitary function, particularly the secretion of LH and FSH, is very limited and that the data which exist are controversial; apparently, while it is known that nicotine may modulate the secretion of hypothalamic CRF, nothing is known about the role of nicotine in the secretion of LHRH from the hypothalamus. I would be very interested in presenting a proposal to your agency to study the following basic points:

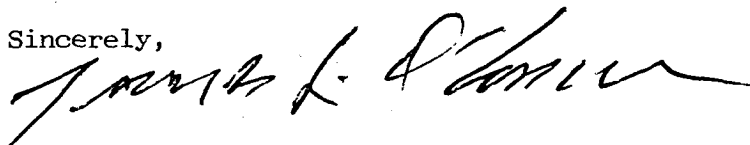
- 1) When nicotine is administered in vivo, what are its effects on the secretion of LHRH exhibited by perfused hypothalami?
- 2) When nicotine is administered in vitro to perfused hypothalami, what are the effects on the secretion of LHRH?
- 3) When nicotine is administered in vivo, what are its effects on in vivo blood levels of LH and FSH?
- 4) When nicotine is administered in vivo, is the response to nicotine variable with the stage of the ovulatory cycle?
- 5) When nicotine is administered in vitro to cultured anterior pituitary cells, what are its effects on the secretion of LH and FSH from these cultures (both basal and LHRH stimulated)?
- 6) In studies (4) and (5), what are the effects of nicotine on the regulation of expression of the gonadotropin subunit genes as indicated by subunit mRNA levels (determined by Northern analysis) and subunit gene transcription rates (determined by transcription run-on assay)?

Dr. McAllister/2-12-93
pg 2

In essence then, the intent of the proposal would be to determine if the gonadotropins respond to nicotine and whether these effects are mediated at the level of the hypothalamus and/or directly at the pituitary. The few studies in the literature which have looked at nicotine and secretion of pituitary hormones have utilized male rats; the proposed studies would utilize female rats in order to focus on the role of nicotine in the secretion of the reproductive hormones in the female. These studies would therefore provide data which are directly applicable to human female tobacco consumers. Would a proposal along these approximate lines be of significant interest to the goals of your agency? My laboratory has documented experience in all the prerequisite protocols needed to conduct the studies. I have included a list of published work so that you might derive a better idea of our competence to conduct studies such as these.

Could you send me literature (application forms, deadlines, review procedures) needed to submit an application? Thank you for your assistance and any suggestions you might have to offer.

Sincerely,



James L. O'Conner, Ph.D.
Department of Physiology and Endocrinology
Medical College of Georgia
Augusta, GA 30912

Phone 706-721-3741
Fax 706-721-7299

jo/enclosure